Cardiovascular Diseases, Susceptibility to Oxidative Injury and Compensatory Mechanisms: Insights from Rodent Models

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Cardiovascular diseases (CVDs) are the number one cause for human mortality. Nearly 25% of the population develops chronic CVD at an age of 65 years or older. Environmental and genetic interactions govern pathogenesis. Increased oxidative stress and compromised antioxidant status are common pathologic factors. Individuals with chronic CVD are deemed more susceptible to environmental exposures, including air pollutants. EPA mandates protection of most vulnerable individuals from harmful effects of pollutants; however, the mechanisms of increased susceptibility are unknown. In this interagency collaborative effort, we asked the following questions: (1) Are rat strains that demonstrate various forms of genetic/polygenic CVD deficient in antioxidant reserve? (2) Does their antioxidant status predict susceptibility to acute ozone-induced oxidative injury? (3) Are there links between susceptibilities to injury from ozone, antioxidants, and gene regulation?

To answer these questions, eight strains of rats, healthy or with CVD known to have increased oxidative stress, were selected. Male 12–15-week-old Sprague Dawley (SD), Wistar (WIS), Wistar Kyoto (WKY), Spontaneously Hypertensive (SH), Stroke-Prone SH (SHSP), Heart Failure Hypertensive (SHHF), Diabetic with CVD (JCR), and Fawn Hooded Hypertensive (FHH) rats were exposed nose-only to ozone (0.0, 0.25, 0.5, or 1.0 ppm for 4 h). Lung, heart, and lung-lining fluid antioxidants (glutathione and ascorbate), cardiac pathology, lung injury/inflammation, and gene expression were analyzed.

Rats with CVD had lower glutathione in the heart but not in the lung relative to healthy ones, suggesting that the organ-specific antioxidant deficiency likely occurs through epigenetic mechanisms. Ozone caused dose-dependent injury and inflammation in all rat strains. Although inflammation is a common phenotype for a variety of diseases, there were wide variations among strains in the baseline expression of lung inflammatory genes. Furthermore, not all diseased strains demonstrated increased expressions, suggesting differential gene regulation in similar disease phenotypes. Lung vascular leakage was greater in SHSP, SHHF, SH, and WIS rats, and neutrophilic inflammation was greater in FHH, WIS, SHSP and WKY rats, suggesting no clear relationship between ozone susceptibility and CVD. Most rat strains responded to ozone exposure by depletion in ascorbate in lung-lining fluid, consistent with ascorbate being a first line of defense. Rats with CVD or with lower antioxidants did not necessarily demonstrate

greater antioxidant depletion or injury. To make genetic linkage to susceptibility in animal models and in humans, variable phenotypes will be evaluated for possible gene mutations which then will be linked to human CVD.

Our results provide insight into understanding the wide variations in human susceptibility to environmental stressors. The relationships among antioxidant levels, underlying CVD, and ozone-induced inflammatory response may not be generalized for all rat strains or disease conditions. Redundancy in biological mechanisms, epigenetic controls, and genetic differences may all play a role in determining susceptibility to environmental stressors. Unraveling these complex relationships using systematic experimental approaches might provide the mechanistic understanding of susceptibility and lead to the development of efficient counter measures in protecting the most vulnerable individuals.

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